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Activation of brain areas concerned with social cognition during moral decisions is abnormal in schizophrenia patients and unaffected siblings

Delfina de Achával [a,b,d,e,1], Mirta F. Villarreal [a,d,e,1], Arleen Salles [f], M. Julia Bertomeu [f], Elsa Y. Costanzo [d,e], Micaela Goldschmidt [d,e], Mariana N. Castro [a,b,d,e], Iris van der Poel [d,e,g,2], Charles B. Nemeroff [h,3], Salvador M. Guinjoan [a,b,c,d,e,*]

[a] National Council of Scientific and Technological Research (CONICET), Av. Rivadavia 1917, Buenos Aires C1033AAJ, Argentina
[b] Department of Mental Health, FLENI Teaching Unit, School of Medicine, University of Buenos Aires, Montañeses 2325 8th Floor, C1428AQK, Argentina
[c] Department of Neurophysiology, School of Psychology, University of Buenos Aires, Hipólito Yrigoyen 3242, Buenos Aires C1207ABQ, Argentina
[d] FLENI, Department of Neurology, Montañeses 2325, Buenos Aires C1428AQK, Argentina
[e] FLENI, Department of Psychiatry, Montañeses 2325, Buenos Aires C1428AQK, Argentina
[f] Centro de Investigaciones Filosóficas, CIF-CONICET, Miñones 2073, Buenos Aires C1428ATE, Argentina
[g] Radboud University, Nijmegen Medical Centre, Nijmegen, The Netherlands
[h] Department of Psychiatry and Behavioral Sciences, Leonard M. Miller School of Medicine, University of Miami, 1120 Northwest 14 St., Suite 1455, Miami, FL 33136, USA

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ABSTRACT

Moral decision-making involves complex social cognitive processes which are known to be altered in patients with schizophrenia and first-degree relatives. Traditional philosophical views on human moral behavior have distinguished between utilitarian views (which emphasize outcomes) and deontological approaches (defining what is right to do according to certain norms). Since emotions have been suggested to play a determining role in moral behavior, we hypothesized patients with schizophrenia and unaffected siblings would make more utilitarian choices and show faulty activation of brain areas concerned with emotion regulation during such tasks. Unexpectedly, all participants ($n = 13$ per group) made the same proportion of utilitarian and deontological decisions. Brain activation common to all groups induced by moral decisions included two circumscribed portions of right ventromedial and dorsolateral prefrontal cortex, adding to previous evidence on a right prosencephalic cognitive network involved in ethical decisions. However, brain activation induced by moral decisions was different in healthy persons, schizophrenia patients, and nonpsychotic siblings in regards to areas directly concerned with emotion processing. These results seem to underscore the role of acquired norms in moral decisions, a frequently overlooked concept in the neurobiological characterization of human ethical behavior, and add to previous evidence of abnormal social cognitive processing in schizophrenia.

1. Introduction

Schizophrenia is defined by the presence of delusions, hallucinations, formal thought disorder, and negative symptoms (American Psychiatric Association, 1994), in addition to neurocognitive, emotion processing, and social cognitive deficits, which are in part inherited and therefore shared by first-degree relatives of patients (de Achával et al., 2010). More complex forms of human interaction in schizophrenia, involving moral decision-making, have received very little attention in the literature (Baruk and Amiel, 1953; Johnson, 1960), with only one recent communication on the topic (Wischniewski and Brüne, 2011). Functional magnetic resonance imaging has become a prominent method of exploration of brain systems in schizophrenia (Gur and Gur, 2010). In particular, different abnormalities of brain activation related to emotion processing and social cognitive tasks have been found in patients with schizophrenia, underlying deficits of actual functioning in these areas (see Gur and Gur, 2010 for a review; de Achával et al., 2012). However, to our knowledge no study has addressed brain activation during moral decision-making in schizophrenia, which has been proposed to be closely related to affective and social cognitive

* Corresponding author. FLENI, Dept. of Mental Health, UBA School of Medicine, Montañeses 2325 8th Floor, C1428AQK Buenos Aires, Argentina. Tel.: +54 11 5777 3200x2824; fax: +54 11 5777 3209.
E-mail addresses: icp.vanderpoel@student.ru.nl (I. van der Poel), CNemeroff@med.miami.edu (C.B. Nemeroff), sguinjoan@fleni.org.ar, sguinjoan@hotmail.com (S.M. Guinjoan).
[1] Both authors contributed equally to this paper.
[2] Tel.: +34 625502752.
[3] Tel.: +1 305 243 6400; fax: +1 305 243 8532.

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processing (Greene et al., 2001; Young et al., 2010a), known to be prominently disturbed in this disorder (see Gur and Gur, 2010 for a review; de Achával et al., 2010; de Achával et al., 2012). Whereas patients with schizophrenia and unaffected first-degree relatives share several social cognitive deficits (de Achával et al., 2010), the presence of abnormalities of moral decision in first-degree relatives of schizophrenia patients have not been reported to our knowledge. Exploring this issue would permit to make inferences on the influence of genetic predisposition to schizophrenia in this regard.

Apart from its importance for further characterization of complex social phenomena in schizophrenia, the study of moral decision-making in siblings discordant for the disease might represent a model to probe the role of emotion processing and social cognition in moral decision-making in general. Traditional philosophical and psychological views on how human beings decide on moral affairs (Piaget, 1965; Turiel, 1983) place emphasis on the role of reasoning, usually in the form of either following certain universal moral rules (i.e., deontological approaches, Kant, 1785, 2004), or the attainment of pleasure and well-being and avoidance of pain (i.e., utilitarian approaches, Bentham, 1907; Mitsis, 1988), or a combination of the two. More recently, some philosophers have proposed that emotions can also play a significant moral role (Blum, 1994; Nussbaum, 1978). There is recent neuroscientific evidence to support such a view (Greene et al., 2001; Haidt, 2001; Damasio, 2007), though experimental data have not been uniform regarding the precise role of emotions in ethical behavior (Nichols and Mallon, 2006). Emotions have been proposed to play a key role in moral decision making in two main contexts. First, a brain emotion processing system integrated at the ventromedial prefrontal cortex (VMPFC) has been posited to be critical to identifying an unsuccessful intent to cause harm as less morally acceptable than actual harm caused by accident (Ciaramelli et al., 2007; Mendez et al., 2005; Young et al., 2010a). Second, the reason why inducing direct personal harm to prevent greater damage is morally less acceptable than indirect personal loss to provoke the same, utilitarian outcome, is believed to be because the former situation evokes a greater emotional response (Greene, 2007). In both cases, it is proposed that faulty emotional processing is causally related to the choice of utilitarian options when faced with moral dilemmas. According to this model, moral actions that result in personal damage are more salient from an emotional perspective and, in this way, affect people's judgment (Greene et al., 2001), even though support for the role in moral judgment of the brain network traditionally considered to subserve emotion and affective processing has not been uniform (Nichols and Mallon, 2006; Baumgartner et al., 2011). The extensive documentation of abnormal emotional processing and social cognitive abilities in patients with schizophrenia makes this group apt to test the role of emotions in moral decision-making. Thus, in order to test the hypothesis that faulty emotional processing results in a tendency to make utilitarian-type responses to moral dilemmas, and to characterize the neural bases for such difference, we compared healthy individuals to patients with schizophrenia, predicting the latter would show a different pattern of moral decision-making and abnormal brain activation induced by ethical dilemmas. To avoid the confounding effects of medications and active psychotic symptoms, we also tested unmedicated, nonpsychotic siblings of schizophrenia patients, who share substantial emotion processing deficits with them (de Achával et al., 2010; de Achával et al., 2012). An additional reason for studying nonpsychotic siblings of patients with schizophrenia is to determine if observed abnormalities are heritable (Preston and Weinberger, 2005). Quantitative biological traits (including patterns of brain activation as revealed by functional MRI) which are shared by patients and unaffected siblings are usually referred to as intermediate phenotypes. A preliminary finding of overlapping abnormalities of brain activation induced by moral decision-making would suggest this might represent an intermediate phenotype, as it has been found in other social cognitive paradigms (Preston and Weinberger, 2005; Gur and Gur, 2010; de Achával et al., 2012). We predicted that patients with schizophrenia and unaffected siblings would make more utilitarian vs. deontological judgments on the basis of faulty emotional processing, as suggested by prior studies (Baruk and Amiel, 1953; Johnson, 1960), and that they would display faulty activation of predominantly right ventromedial prefrontal cortex (Young and Koenigs, 2007), insula, temporoparietal junction, and anterior cingulate (Sanfey et al., 2003; Young et al., 2010b; de Achával et al., 2012) when confronted with ethical dilemmas. We also reasoned that activation of such areas in the experimental groups would be more divergent from the normal pattern when moral decisions attained by participants were utilitarian (i.e., those predicted to be more characteristic of experimental groups) instead of deontological.

2. Methods and materials

2.1. Participants

Two psychiatrists (SMG, EYC) and a psychologist (DdA) assessed all participants, who were seen at the Cognitive Neurology Section and the Psychiatry Department at FLENI Hospital, Buenos Aires. All participants were right-handed and provided written informed consent as approved by the local bioethics committee, in accordance with the ethical standards set by the 1964 Declaration of Helsinki. A family member of patients was also requested to provide written consent.

2.1.1. Patients

Outpatients at the Departments of Neurology and Psychiatry (Table 1) were invited to participate in the study if they (a) fulfilled DSM-IV-TR diagnosis of schizophrenia, any subtype, confirmed with a Composite International Diagnostic Interview (Robins et al., 1988) administered by a consultant psychiatrist (EYC), (b) were aged 18–50 years, and (c) had been on the same medication plan for at least two weeks. Exclusion criteria were (a) use of illegal substances in the previous 6 months, (b) active symptoms having recently (<2 weeks) warranted antipsychotic dose adjustment or admission to the hospital, day hospital, or intensive outpatient treatment, or (c) a history of mental retardation. Current symptom severity was assessed with the Positive and Negative Syndrome Scale (Kay et al., 1987).

2.1.2. Siblings

Siblings (Table 1) were recruited from families of patients participating in this study ($n = 7$), and from families with affected members who did not fulfill the symptom stability criterion ($n = 6$). Exclusion criteria included (a) use of illegal substances in the previous 6 months (b) the lifetime presence of any DSM-IV-TR Axis I psychotic disorder diagnosis as detected by a psychiatric interview with the consultant psychiatrist (EYC) and (c) a medication history of antipsychotics, antidepressants, or mood stabilizers. Siblings were not found to have experienced Axis I Mood and Anxiety disorders in the clinical interview.

2.1.3. Controls

Healthy comparison individuals (Table 1) were recruited from the local community. Exclusion criteria included (a) use of illegal substances in the previous 6 months (b) the lifetime presence of any DSM-IV-TR Axis I anxiety, mood, or psychotic disorder diagnosis as detected by a psychiatric interview with a psychiatrist (EYC) and (b) a medication history of antidepressants, antipsychotics, or mood stabilizers.

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Table 1
Demographic and clinical data, MATRICS Consensus Cognitive Battery scores, and latency and type of choice to moral dilemmas.

	Patients ($n = 13$)	Siblings ($n = 13$)	Controls ($n = 13$)	Statistic	p
Age (years)	30.7 ± 7.3	30.7 ± 4.8	28.5 ± 8.6	$F = 0.429$	0.654
Education (years)	14.1 ± 2	15.2 ± 2.5	15.1 ± 1.8	$F = 1.045$	0.362
Parental education (years)	11 ± 3.7	12.8 ± 3.4	13.7 ± 3.6	$F = 1.858$	0.171
Women, *n* (%)	1 (8)	5 (39)	5 (39)	$X^2 = 4.05$	0.132
Age at onset (years)	23.8 ± 4.9				
Disease duration (years)	7.7 ± 4.7				
MMSE score	28.9 ± 1.5	28.8 ± 1.4	29.5 ± 0.9	$F = 1.372$	0.267
WAT score	31.7 ± 3.6	32.9 ± 5.7	33.5 ± 7.8	$F = 0.292$	0.749
MCCB (percentile)					
Speed of processing	4 ± 10[b]	28 ± 27	46 ± 23	$F = 12.705$	<0.001
Attention/vigilance	17 ± 22[b]	26 ± 30[a]	54 ± 23	$F = 7.643$	0.002
Working memory	18 ± 19[a]	38 ± 34	60 ± 25	$F = 8.047$	0.001
Verbal learning	24 ± 22[a]	30 ± 31	54 ± 28	$F = 4.343$	0.020
Visual learning	30 ± 29	48 ± 41	57 ± 28	$F = 2.197$	0.126
Reasoning/problem solving	15 ± 23[b]	21 ± 18[a]	47 ± 31	$F = 6.444$	0.004
Social cognition	22 ± 28[b]	32 ± 34[a]	62 ± 28	$F = 6.267$	0.005
MCCB total score	7 ± 19[b]	26 ± 26[a]	56 ± 25	$F = 14.129$	<0.001
Symptom severity					
PANSS, positive	13.4 ± 6.7				
PANSS, negative	21.2 ± 7.7				
PANSS, total	70.6 ± 21.5				
Hamilton depression score	6.5 ± 4.4[a]	3.2 ± 3.6	1.7 ± 2.1	$F = 6.460$	0.004
Hamilton anxiety score	9.5 ± 6.1[b]	5 ± 4.6	2.4 ± 2.3	$F = 8.986$	0.001
Medications					
Valproic acid, *n* (%)	1 (7.7)				
Risperidone, *n* (%)	5 (38.5)				
Olanzapine, *n* (%)	2 (15.4)				
Clozapine, *n* (%)	1 (7.7)				
Quetiapine, *n* (%)	3 (23.1)				
Paliperidone, *n* (%)	4 (30.8)				
CMZ equivalent (mg/day)	240 ± 150				
SSRI, *n* (%)	6 (46.1)				
Benzodiazepine, *n* (%)	8 (61.5)				
Response latency (s)					
Moral dilemmas	5.2 ± 1.1	5.4 ± 1.1	4.4 ± 0.9	$F = 3.197$	0.053
Non-moral dilemmas	5.5 ± 1	5.3 ± 1	4.7 ± 0.7	$F = 2.766$	0.077
Response type (%)					
Deontological	71.4 ± 15.4	77.6 ± 19.5	77.4 ± 8.3	$F = 0.684$	0.511
Utilitarian	27.1 ± 15.4	22.9 ± 18.9	23.6 ± 9.9	$F = 0.268$	0.767

Shown are mean ± standard deviation or number (%). MMSE: Mini-Mental Status Examination; WAT: Word Accentuation Test; MCCB: MATRICS Consensus Cognitive Battery; PANSS: Positive and Negative Symptom Scale; CMZ: Chlorpromazine; SSRI: Specific Serotonin Reuptake Inhibitor.
[a] Different from controls.
[b] Different from the other groups, post hoc HSD Tukey's test.

2.2. Neurocognitive screening measures

2.2.1. Cognitive measures

Within 24 h prior to fMRI studies, general cognitive functioning was measured in all participants with the MATRICS Consensus Cognitive Battery (MCCB; Kern et al., 2008; Nuechterlein et al., 2008) and Mini Mental State Examination (MMSE; Folstein et al., 1975). Premorbid intelligence was estimated with the Word Accentuation Test (WAT; Del Ser et al., 1997; de Achával et al., 2012).

2.2.2. Mood status measures

Subjects were also assessed for depression symptom severity with the Hamilton Depression Rating Scale (Hamilton, 1960) and for anxiety symptom severity with the Hamilton Anxiety Rating Scale (Hamilton, 1969) prior to the fMRI session.

2.3. fMRI stimuli

2.3.1. Moral Dilemmas Test (MDT)

We used a modified version of the Moral Dilemmas Test (Greene et al., 2001), including personal, impersonal and non-moral dilemmas. A battery of 32 scenarios divided into two sessions were visually presented as short passages in which the subject had to judge the character's action based on a dilemma, while undergoing brain scanning using fMRI. Scenarios in each session were equally divided into two conditions: "moral" dilemmas (experimental condition) and "non-moral" dilemmas (control condition). These scenarios were based on those used in the Greene et al. (2001) study. We used a block design paradigm. Each session consisted in 4 blocks with 4 scenarios of 30 s each. Half of the blocks were an experimental condition and the other half a control condition. Stimuli were presented on a visual display projected into the scanner. Each scenario was presented as text through a series of three screens, the first one describing a situation, the second one exposing a dilemma based on the previous situation, and the third one posing a question about the appropriateness of an action one might perform in that scenario. Each screen was presented for 10 s and each scenario was followed by a 3 s fixation cross. In this paradigm, there are nocorrect answers. In the experimental condition, responses were related to a utilitarian or deontological solution to a moral dilemma, for example: "A runaway trolley is headed for seven people who will be killed if it proceeds on its present course (1st screen)", "the only way to save them is to hit a switch that will turn the trolley onto an alternate set of tracks where it will kill one person instead of seven (2nd screen)", "Would you consider appropriate to turn the trolley in order to save seven people at the expense of one? (3rd. screen)." After reading the third screen participants responded by pressing one of two buttons ("yes" or "no") with the index or middle fingers

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of the right hand. In this paradigm, a moral decision is considered utilitarian if the participant decides to risk a person's life in order to save more lives. On the contrary, a decision is considered deontological if the participant does not make such decision because it is wrong to do so, even though its outcome would be "useful" in terms of saving more lives.

In the control condition, the subject responses were related to a decision without moral content, such us traveling to the coast by a side road with a nice landscape vs. choosing a faster highway with no views.

All the stimuli were presented via Presentation®. Subjects were trained with an example of each condition before scanning. The examples used for training were not displayed again in the scanner. The two sessions were presented in a counterbalanced order, and there was a short break between them but the subject did not leave the scanner or move.

2.4. fMRI data acquisition

MRI data were acquired on a 3T General Electric HDx scanner with an 8 channel head coil. Change in blood-oxygenation-level-dependent (BOLD) T2* signal was measured using a gradient echo-planar imaging (EPI) sequence. Thirty contiguous slices were obtained in the AC–PC plane (TR: 2.37 s, TE: 30 ms, flip angle: 90°, FOV: 24 cm, 64 × 64 pixels per inch matrix, voxel size = 3.75 × 3.75 × 4). A structural MRI was acquired with the fast SPGR-IR sequence (120 slices, 1.6-mm thick slices, TR 12.956 ms, TE 6.1 ms, flip angle 15°, FOV 24 cm, 512 × 512 matrix). Two sessions of 235 volumes were taken per subject.

2.5. Statistical analysis

2.5.1. Analysis of behavioral data

Discrete variables in patients, siblings and controls were compared using a chi-square test, and continuous variables were compared using a one–way ANOVA followed by a Tukey HSD test. Significance was assumed at $\alpha < 0.05$, and all reported results were two-tailed. All tests were performed with the SPSS version 13.0 software (SPSS Inc.).

2.5.2. fMRI analysis

2.5.2.1. Image processing. Image processing was carried out using SPM 8 (Wellcome Department of Cognitive Neurology, London, UK) implemented in MATLAB 11 (Mathworks Inc., Sherborn, MA, USA). Slice-timing correction was applied to each volume. The imaging time series was realigned to the first volume and spatially normalized to the stereotactic space of Talairach and Tournoux (1988) using Montreal Neurological Institute reference brain (Ashburner and Friston, 1999). The normalized volumes of 2 × 2 × 2 mm^3 were spatially smoothed by an isotropic Gaussian kernel of 8 mm at full width half-maximum (Friston et al., 2000).

2.5.2.2. Statistical analysis. Individual analysis was computed using the general linear model including the control and experimental conditions as individual regressors of interest for each screen. Our interest in the present study was to determine the neural patterns of moral decision-making, tested in the third screen of each dilemma where the participant must determine if the protagonist's action is appropriate or not.

The effects were modeled using a canonical hemodynamic response function. The design matrix also included correction for head movements. A linear contrast MORAL–NO MORAL for each screen was applied to the design in every subject and these individual contrast images were subjected to a random effect analysis to see effects at a group level.

Differences between groups were analyzed with an ANOVA test for PATIENTS vs. CONTROLS, SIBLINGS vs. CONTROLS, and PATIENTS vs. SIBLINGS, and areas in common between samples were observed with a conjunction analysis using the conjunction null inference (Nichols et al., 2005), which tested the null hypothesis that *one or more* of the effects were null (non-zero), equivalent of having a logical AND between groups. This required that all comparisons in the conjunction be individually significant. A second analysis was computed at an individual level using a new model dividing the experimental condition into utilitarian and deontological choices. Two linear contrasts were performed in this case: UTILITARIAN − NO MORAL and DEONTOLOGICAL − NO MORAL. The number of events subtracted was balanced between the two tasks. These individual contrasts images were subjected to a new random effect analysis.

For all the group's operations we used a statistical threshold of $p < 0.05$ corrected FDR and a cluster size of 10 voxels.

3. Results

3.1. Behavioral results

Patients with schizophrenia, unaffected siblings, and healthy controls were comparable in terms of age, sex, years of education, years of parental education, general intelligence, and basic cognitive screening (Table 1). As previously described (de Achával et al., 2012), patients had lower performance than controls in various neurocognitive dimensions as assessed in greater detail by means of the MCCB, a battery designed for the detection of specific cognitive deficits in schizophrenia patients (Kern et al., 2011). Patients' nonpsychotic siblings were similar to controls in this regard, except that they displayed lower attention, problem solving, and social cognitive abilities (Table 1).

3.2. fMRI results

Utilitarian responses represented almost a quarter of responses to moral dilemmas in all three groups (Table 1), with deontological decisions being the rest. There were no differences between groups in this regard. In all groups response times were similar for both types of decision (Table 1).

Fig. 1 depicts brain activation patterns in healthy individuals (top panel), patients with schizophrenia (middle panel) and nonpsychotic siblings (bottom panel) when challenged with a moral dilemma requiring a response. Healthy controls display predominant activation in bilateral anterior and posterior insula, bilateral superior temporal gyrus (STG), right middle frontal gyrus (MFG), and anterior cingulate (ACC; Fig. 1, top panel). In patients, activation occurred in left ventromedial PFC (VMPFC), bilateral areas of the dorsomedial PFC (DMPFC), and right ACC (Fig. 1, middle panel). Areas of activation in nonpsychotic siblings of patients included left dorsolateral PFC (DLPFC), right posterior VMPFC, left STG, and and bilateral occipital cortex. Table 2 shows the main coordinates and the statistical values of the areas described above.

Fig. 2 shows contrasts between experimental groups and healthy participants; A panels show areas of increased activation in controls compared to experimental groups (or siblings compared to patients in the bottom panel), and B panels depict areas of increased activation in experimental groups compared to controls (or in patients compared to siblings in the bottom panel). In general, comparisons reveal that brain activation in schizophrenia patients and nonpsychotic siblings were remarkably similar. Compared with either patients with schizophrenia (Fig. 2A, top panel) or unaffected siblings (Fig. 2A, middle panel), healthy participants showed stronger activation of the right hippocampus. Patients and siblings showed increased activation in the superior frontal (Fig. 2B,

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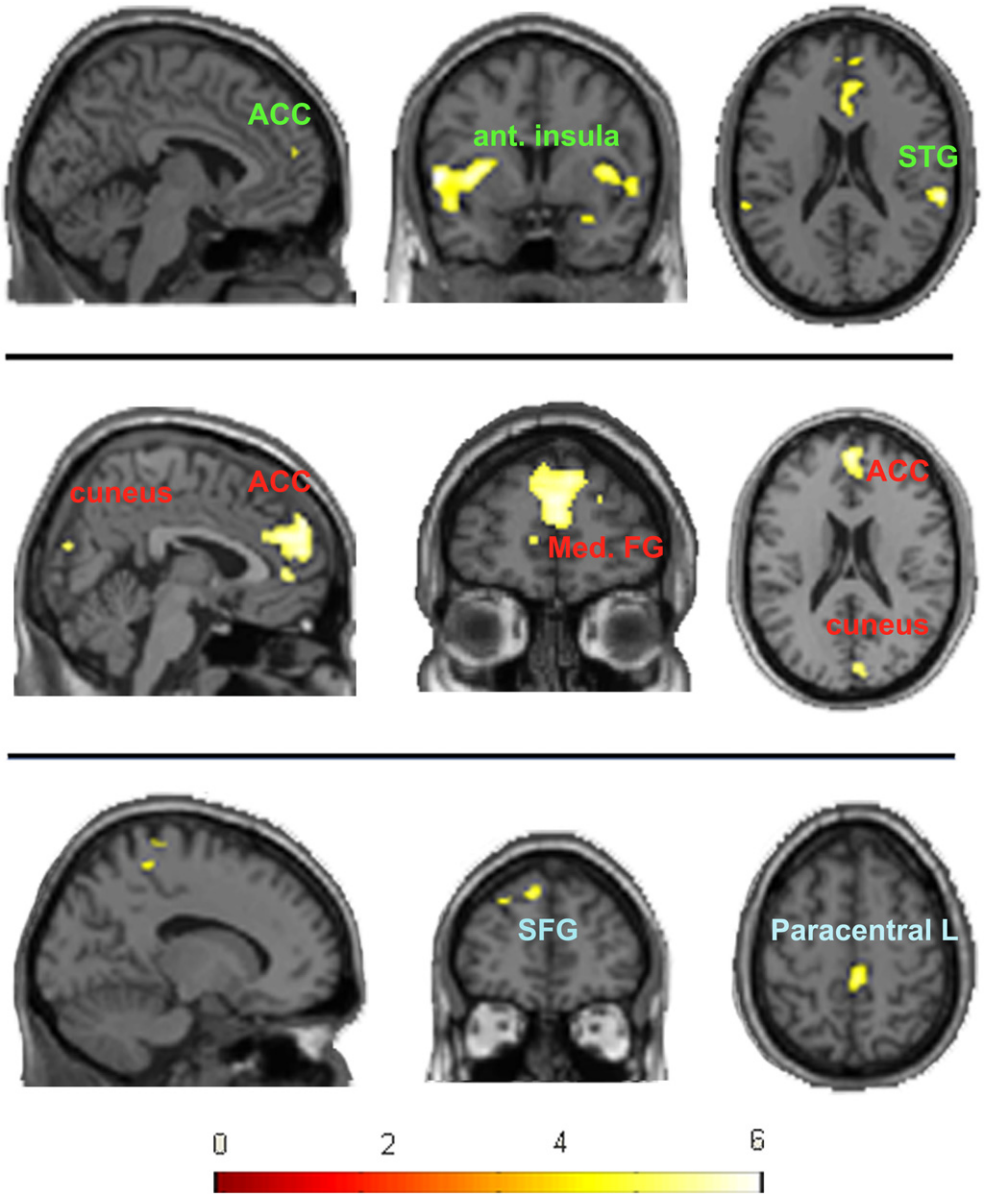

Fig. 1. Group analysis of brain activation patterns in healthy individuals (top panel), patients with schizophrenia (middle panel) and nonpsychotic siblings of patients with schizophrenia (bottom panel) when challenged with a moral dilemma requiring a response. Coordinates displayed are: $x = -4$, $y = 4$, $z = 20$ for controls; $x = 4$, $y = -65$, $z = 20$ for patients; and $x = -14$, $y = 46$, $z = 56$ for siblings. ACC: Anterior cingulate cortex; STG: Superior temporal gyrus; SFG: Superior frontal gyrus; MOG: Middle occipital gyrus.

top panel) and inferior frontal gyri (Brodmann's area 44, pars opercularis, Fig. 2B, middle panel), respectively. Compared to patients, nonpsychotic siblings showed activation in a portion of the right precuneus (Fig. 2A, bottom panel) and patients presented increased activation in the right STG (Fig. 2B, bottom panel).

Fig. 3 shows overlapping areas of brain activation in all three groups, namely two relatively small areas in the rVMPFC and rDLPFC. No common activation areas in other limbic or prefrontal structures concerned with emotion processing were detected.

Fig. 4 depicts patterns of brain activation associated to utilitarian (left panels) or deontological (right panels) types of responses to moral dilemmas in healthy participants (top), patients with schizophrenia (middle), and nonpsychotic siblings of schizophrenia patients (bottom). Healthy participants displayed similar patterns of brain activation irrespective of the type of moral choice, although deontological decisions were associated with relatively larger areas of activation in bilateral insular cortex and inferior frontal gyri (Fig. 4, top panel). Strong activation of bilateral supplementary motor area (SMA) was present in both types of moral decision when contrasted with nonmoral choices, in healthy individuals and both experimental groups (Fig. 4). Patients showed activation of medial portions of cerebellar hemispheres (Fig. 4, middle panel) and controls showed activation of caudate nucleus (Fig. 4, top panel). In patients, brain activation beyond SMA and cerebellum occurred only during deontological decisions, and included bilateral —predominantly right- superior temporal gyri extending onto OF cortex (Fig. 4, middle panel). A similar pattern was observed in siblings but encompassing more circumscribed areas, especially in the right cerebral hemisphere (Fig. 4, bottom panel).

4. Discussion

To our knowledge, this is the first study describing brain activation patterns associated with ethical decision-making in patients

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Table 2
Coordinates of the areas activated in patients with schizophrenia, unaffected siblings, and healthy controls.

Region	Peak activation			Cluster volume	*t* value
	x	*y*	*z*	(*n* voxels)	
Controls					
Superior temporal gyrus BA 42	64	−30	20	194	5.17
Left insula BA13	−38	12	6	425	4.76
Right insula BA13	38	6	6	68	4.42
Right anterior cingulate BA24	4	20	24	115	4.40
Left superior temporal gyrus BA22	−58	−28	6	83	4.21
Right middle frontal gyrus BA8	26	38	42	13	4.12
Patients					
Right medial frontal gyrus BA9	2	52	24	1137	4.47
Left superior frontal gyrus BA 6	−14	22	62	1137	4.44
Right anterior cingulate BA 32	4	46	4	54	3.89
Right cuneus BA18	6	−86	20	35	3.87
Left medial frontal gyrus BA10	−10	54	6	10	3.58
Siblings					
Left superior frontal gyrus BA 8	−24	42	46	37	4.96
Left medial frontal gyrus BA9	−2	32	30	19	3.93
Right cuneus BA19	4	−90	30	16	3.74
Right middle frontal gyrus BA 9	26	38	36	10	3.65

with schizophrenia and nonpsychotic siblings, who are known to share deficits in emotion processing. The main findings are that 1) when confronted with moral decisions, patients with schizophrenia and unmedicated, nonpsychotic siblings have an almost identical profile of moral choices in the present paradigm (i.e., a quarter of utilitarian vs. three quarters of deontological choices), compared with healthy subjects of a similar background, and 2) siblings discordant for schizophrenia display a different brain activation profile as compared to healthy subjects, except for two circumscribed areas of the right VMPFC and right DLPFC.

The present results do not support one of the primary hypotheses of the study, i.e. that patients with schizophrenia and at-risk subjects make moral decisions distinct from those by healthy persons on the basis of their extensively documented deficits in emotion processing and theory of mind (de Achával et al., 2010; de Achával et al., 2012). Specifically, our results are different from a study on ethical decision-making performed before the advent of antipsychotic medication (Baruk and Amiel, 1953), in that our sample of patients did not show an excess of utilitarian choices when confronted with moral dilemmas. Another study, published a few years after the introduction of chlorpromazine, the first antipsychotic agent, incorporated a heterogeneous sample of patients (Johnson, 1960). Some participants in that study were "predischarge schizophrenics" and produced a similar percentage of utilitarian responses as compared to controls, much like the

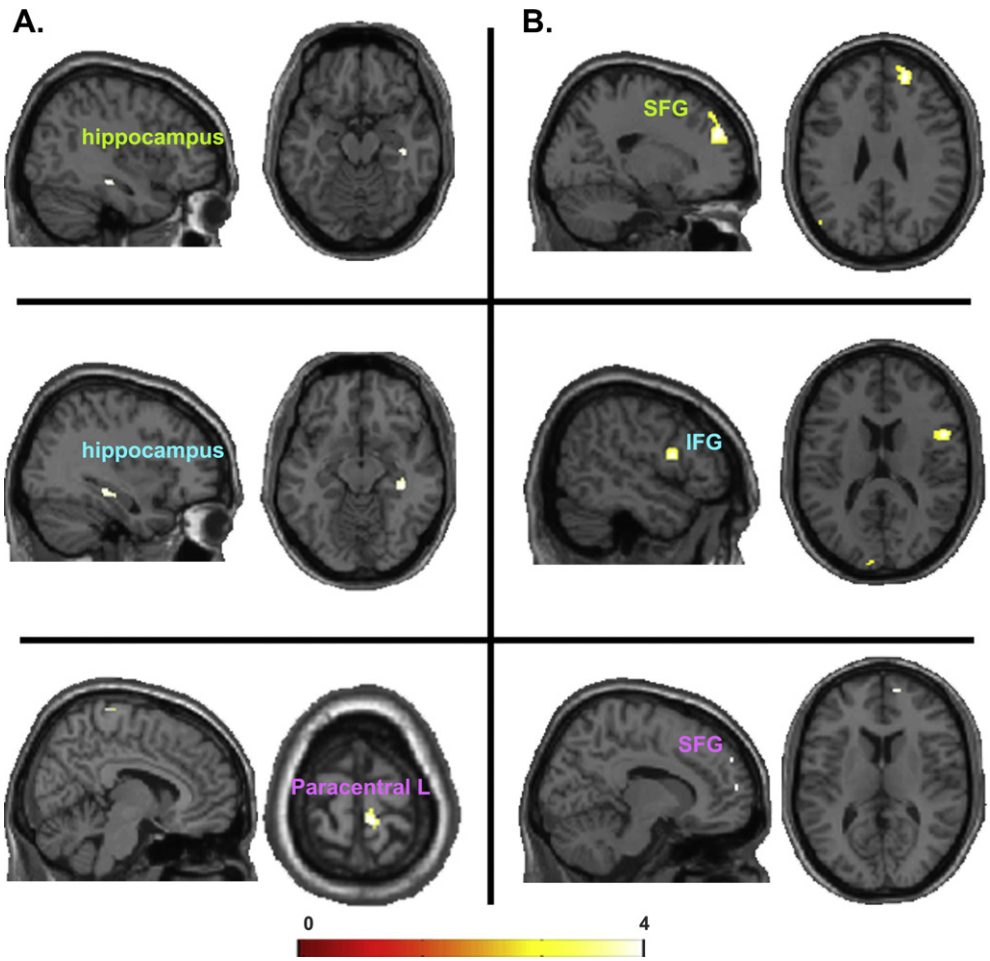

Fig. 2. Anova between groups. Top panel: A. Healthy subjects vs. patients, coordinates $x = 36$, $z = -12$, B. patients vs. healthy subjects, $x = 20$, $z = 28$. Middle panel: A. Healthy subjects vs. siblings, coordinates $x = 36$, $z = -12$, siblings vs. healthy subjects, coordinates $x = 52$, $z = 16$. Bottom panel: A. Siblings vs. patients, coordinates $x = 8$, $z = 76$, B. patients vs. siblings, coordinates $x = 14$, $z = 12$. IFG: Inferior frontal gyrus; SFG: Superior frontal gyrus.

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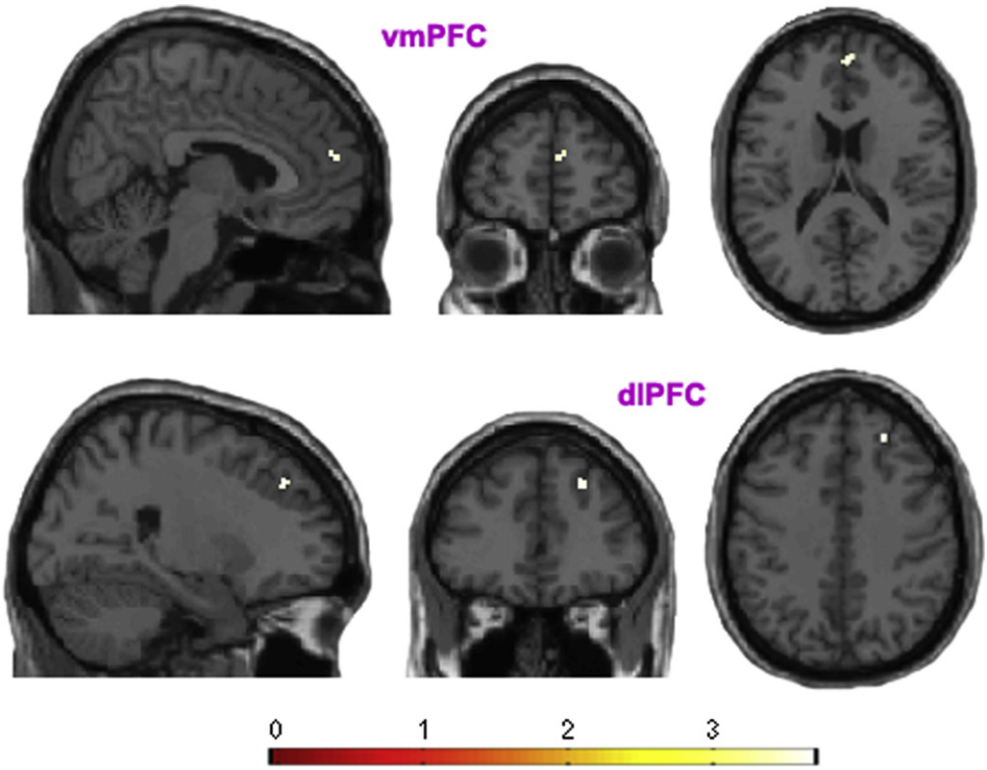

Fig. 3. Conjunction analysis in the three groups. Coordinates are: $x = 24$, $y = 38$, $z = 40$ (top); $x = 6$, $y = 56$, $z = 18$ (bottom). L: Lobule; TP: Temporal pole.

present results. We hypothesize such patients might have represented a subsample of individuals who had improved enough to permit discharge from the hospital by virtue of effective antipsychotic treatment, making it comparable to our sample. Moreover, the type of moral choices made by patients with schizophrenia treated for their condition might help to explain why according to recent epidemiological evidence, they do not engage in unlawful behavior at higher rates than the general population (Fazel et al., 2009; Nielsen and Large, 2010). Recent findings in a different paradigm also concerned with ethical decision-making (Wischniewski and Brüne, 2011) also support the view that patients schizophrenia have normal decision-making abilities concerning moral aspects of human relationships.

Our results provide support to the opinion that the VMPFC has a critical role in the production of moral choices. In addition, we identified the simultaneous activation of a small area in the rDLPFC, which has been demonstrated to be functionally related with VMPFC in paradigms where subjects are confronted with acceptance of an unfair offer (Baumgartner et al., 2011). Whereas these conjunction findings were relatively weak probably due to the small sample size, if confirmed in additional samples, our observation of simultaneous activation of right DLPFC and VMPFC in all three groups —who also coincide in the type of moral choices- supports the view that these areas are involved in deciding between an option which is useful but unfair according to a certain norm (e.g., killing a person so as to save five, analogous to accepting an unfair amount of money in Baumgartner et al., 2011; study) and a fair, but impractical option (i.e. not killing a person to save five individuals, because it is morally unacceptable, analogous to not accepting an unfair monetary offer because it violates a norm, even though such decision implies relinquishing a financial benefit).

On the other hand, our results confirm previous observations associating activation of areas typically involved in affective regulation (vicinity of TPJ, ACC, and insula) with moral-decision making in healthy individuals. However, the lack of activation of those areas in schizophrenia patients and unaffected siblings, who made almost identical moral decisions as controls, suggests that there might be different paths to making moral choices in humans. This raises the possibility that activation in brain areas subserving emotional processing and social cognition may represent epiphenomena triggered in tested subjects when confronted with moral dilemmas, including personal dilemmas (Greene et al., 2001). These observations are also in line with those by Baumgartner et al. (2011), who demonstrated that areas previously associated with unfair offers, namely ACC, anterior insula, and inferior frontal gyrus, are not causally related to an individual's proneness to reject a convenient but unfair offer, on the basis of moral norms.

Regarding the type of moral decision, when contrasts between nonmoral choices and either deontological or utilitarian decisions were performed in the three groups, we observed that activation of motor planning areas (namely, SMA and medial sectors of cerebellar hemispheres) was present in all cases. Deontological decisions were associated with activation of additional areas, especially in healthy individuals. Since moral choices differed from nonmoral choices in that the former usually involved simple motor actions (e.g., pulling a lever, covering someone's mouth, etc.), SMA and cerebellar activation may reflect the brain functional correlate of imagining such motor actions. Alternatively, SMA has been considered part of a "pain network" activated by aversive or unpleasant salient stimuli (Decety and Michalska, 2010), and in inconvenient but "right" decisions which minimize future guilt feelings (Chang et al., 2011). Regarding the activation of additional areas in deontological choices, it may be that such activation reflects either a posteriori emotional phenomena, or a priori emotional phenomena conditioning the actual choice made by the participant. Again, the discordance in brain activation between the three groups in spite of almost identical moral choices argues against the latter option.

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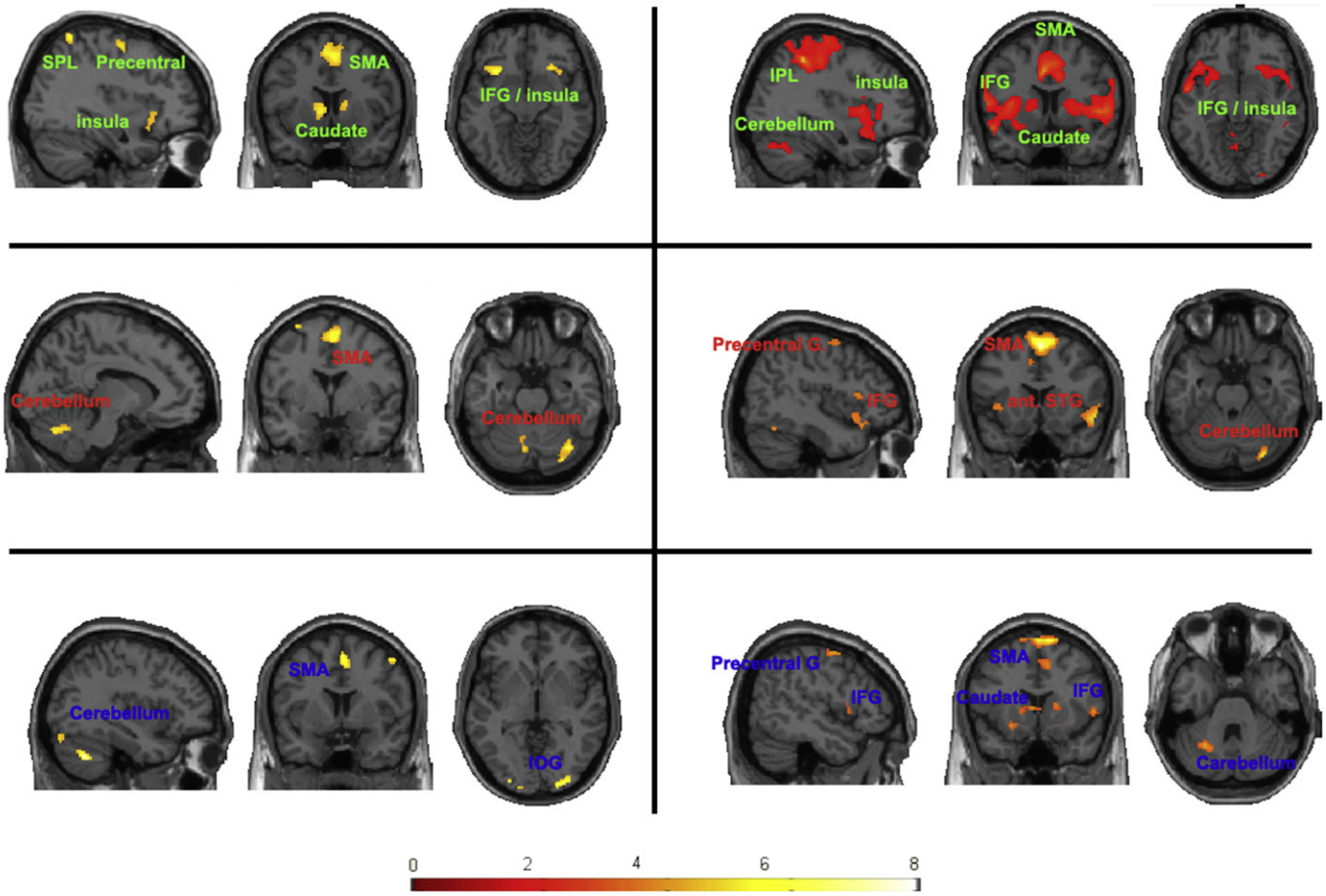

Fig. 4. Brain activation associated to utilitarian (left panels) or deontological (right panels) types of responses to moral dilemmas in healthy participants (top), patients with schizophrenia (middle), and nonpsychotic siblings of schizophrenia patients (bottom). Coordinates for the left panel are: $x = 36$, $y = 8$, $z = -10$ (controls); $x = -23$, $y = 0$, $z = -25$ (patients); $x = -36$, $y = 6$, $z = -3$ (siblings). Coordinates for the right panel are: $x = 36$, $y = 8$, $z = -10$ (controls); $x = 44$, $y = 15$, $z = -24$ (patients); $x = 50$, $y = 14$, $z = -31$ (siblings).

Several limitations of the present study should be considered. First, the present patient sample was recruited from a single clinical center and was culturally and ethnically homogeneous. Culture is known to influence moral decisions, so the present results may not be readily generalizable to other settings. Second, medications (see Table 1) in patients might have influenced functional brain imaging results, although this does not apply to unaffected siblings, who did not receive pharmacological treatment. Third, the number of participants did not permit discrimination of the influence of sex and clinical subtype of schizophrenia in the results, and there is evidence that these two factors account for significant heterogeneity of the disease. Fourth, siblings discordant for schizophrenia not only differed from controls in their emotional processing but also on a number of subtle neurocognitive deficits. Whereas discrepant brain areas activated during moral decisions coincide with those involved in emotion processing, we cannot rule out that neurocognitive deficits might have accounted for different profiles of brain activation as well. Last, the ratio of utilitarian vs. deontological choices is only one way to judge whether moral decision-making is affected in schizophrenia; since only one testing paradigm was used herein, the present results may not be readily applied to moral judgment in schizophrenia in general.

In sum, the common activation of areas in the rVMPFC and rDLPFC probably helps to further define the areas critically involved in moral decision-making. In our view, these results probably underscore the importance of norms in human moral behavior, irrespective of the emotional reactions evoked by the dilemmas the subject is confronted with. Preexisting ethical rules independent from emotional phenomena, and probably determined at least in part by cultural and ethnic background, have been frequently overlooked and thus deserve further exploration in future studies (Nichols and Mallon, 2006; Baumgartner et al., 2011). Even more important, the present results add to burgeoning evidence that different aspects of social cognition display a distinct processing in patients of schizophrenia and persons who are at risk for the disease. A differential processing of ethical decisions in patients with schizophrenia and nonpsychotic siblings of patients may be an important dimension of deficits associated with this disorder.

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CONICET, Agencia de Promoción-MINCYT, and University of Buenos Aires had no role in the design of the study and writing of the manuscript.

Contributors

DdA, MFV, AS, MJB, CBN, and SMG designed the study. DdA, MFV, EYC, MG, MNC, IvdP, and SMG evaluated the participants and performed the experiments. DdA, MFV, and SMG analyzed the data. DdA, MFV, AS, MJB, and SMG wrote the first draft of the manuscript. All authors contributed to and approved the final version of the manuscript.

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Conflict of interest

CBN is a consultant to Xhale and Takeda, is a stockholder of CeNeRx BioPharma, NovaDel Pharma, Inc., PharmaNeuroBoost, Revaax Pharma, and Xhale, he is the owner of patents for method and devices for transdermal delivery of lithium (US 6,375,990B1) and method of assessing antidepressant drug therapy via transport inhibition of monoamine neurotransmitters by ex vivo assay (US 7,148,027B2), he is in the board of directors of AFSP, NovaDel Pharma, Inc., and is in the scientific advisory board of American Foundation for Suicide Prevention (AFSP), CeNeRx BioPharma, National Alliance for Research on Schizophrenia and Depression (NARSAD), NovaDel Pharma, Inc., PharmaNeuroBoost, Anxiety Disorders Association of America (ADAA). All other authors report no conflict of interest.

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